

PTO/SB/08B (07-05)

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| Substitute for form 1449/PTO | | | | Complete if Known | |
| SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary) | | | | Application Number | 10/698,928 |
| | | | | Filing Date | October 31, 2003 |
| | | | | First Named Inventor | Serge Boyer |
| | | | | Art Unit | 1626 |
| | | | | Examiner Name | Solola, Taofiq A. |
| Sheet | 1 | of | 2 | Attorney Docket Number | 2358.0180002/RWE/AES |

| NON PATENT LITERATURE DOCUMENTS | | | | |
|---------------------------------|-----------------------|--|--|----------------|
| Examiner Initials* | Cite No. ¹ | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume issue number(s), publisher, city and/or country where published | | T ² |
| YD | J1 | BRAESS, J. et al. "Oral Cytarabine Octosfate in Acute Myeloid Leukemia and non-Hodgkin's Lymphoma - Phase I/II Studies and Pharmacokinetics", <i>Leukemia</i> 12:1618-1626, Stockton Press (1998) | | |
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| Examiner Signature | T. A. Solola | Date Considered | 3-2-06 |
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| Sheet | 2 | of | 2 | | |

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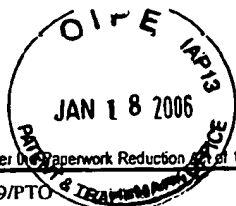
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| U.S. PATENT DOCUMENTS | | | | | |
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| Examiner Initials* | Cite No. ¹ | Document Number | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear |
| | | Number-Kind Code ² (if known) | | | |
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| Examiner Initials* | Cite No. ¹ | Foreign Patent Document | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear | T ⁶ |
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| | FK | WO 96/01267 A1 | 01/18/1996 | Takeda Chemical Ind., Ltd. | | |
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| ✓ | FM | WO 00/52015 A2 | 09/08/2000 | Metabasis Therapeutics, Inc. | | |

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| NON PATENT LITERATURE DOCUMENTS | | | |
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| Examiner Initials* | Cite No. ¹ | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume issue number(s), publisher, city and/or country where published | T ² |
| YD | FN | ALEXANDER, P., et al., "Preparation of 9-(2-Phosphonomethoxyethyl) Adenine Esters as Potential Prodrugs," <i>Collect. Czech. Chem. Commun.</i> 59:1853-1869, Czech Academy of Sciences, Institute of Organic Chemistry and Biochemistry (1994) | |
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| Y0 | FX | BRILL, T. and Landon, S.J., "Arbuzov-like Dealkylation Reactions of Transition-Metal-Phosphite Complexes," <i>Chem. Rev.</i> 84:577-585, American Chemical Society (1984) | |
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| YD | GH | DE LOMBAERT, S., et al., "Pharmacological Profile of a Non-Peptidic Dual Inhibitor of Neutral Endopeptidase 24.11 and Endothelin-Converting Enzyme," <i>Biochem. Biophys. Res. Commun.</i> 204:407-412, Academic Press, Inc. (1994) | |
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| | GK | DICKSON, J.K., et al., "Orally Active Squalene Synthase Inhibitors: Bis((acyloxy)alkyl) Prodrugs of the α -Phosphonosulfonic Acid Moiety," <i>J. Med. Chem.</i> 39:661-664, American Chemical Society (1996) | |
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| | GM | ENRIQUEZ, P., et al., "Conjugation of Adenine Arabinoside 5'-Monophosphate to Arabinogalactan: Synthesis, Characterization, and Antiviral Activity," <i>Bioconjugate Chem.</i> 6:195-202, American Chemical Society (1995) | |
| | GN | ERION, M., et al., "Design, Synthesis, and Characterization of a Series of Cytochrome P ₄₅₀ 3A-Activated Prodrugs (HepDirect Prodrugs) Useful for Targeting Phosph(on)ate-Based Drugs to the Liver," <i>J. Am. Chem. Soc.</i> 126:5154-5163, American Chemical Society (April 2004) | |
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| | | Filing Date | October 31, 2003 |
| | | First Named Inventor | Serge Boyer |
| | | Art Unit | 1626 |
| | | Examiner Name | Solola, Taofiq A. |
| | | Attorney Docket Number | 2358.0180002/RWE/AES |
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| YD | GR | FARQUHAR, D., et al., "Biologically-Cleavable Phosphate Protective Groups: 4-Acyloxy-1,3,2-Dioxaphosphorinanes as Neutral Latent Precursors of Dianionic Phosphates," <i>Tetrahedron Lett.</i> 36:655-658, Elsevier Science Ltd. (1995) | |
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| | GX | FIUME, L., et al., "Inhibition of Hepatitis B Virus Replication by Vidarabine Monophosphate Conjugated with Lactosaminated Serum Albumin," <i>The Lancet</i> 2:13-15, The Lancet Publishing Group (1988) | |
| | GY | FREED, J.J., et al., "Evidence for Acyloxymethyl Esters of Pyrimidine, 5'-Deoxyribonucleotides as Extracellular Sources of Active 5'-Deoxyribonucleotides in Cultured Cells," <i>Biochem. Pharm.</i> 38:3193-3198, Elsevier Inc. (1989) | |
| | GZ | FRIIS, G.J. and Bundgaard, H., "Prodrugs of phosphates and phosphonates: Novel lipophilic α-acyloxyalkyl ester derivatives of phosphate- or phosphonate containing drugs masking the negative charges of these groups," <i>Eur. J. Pharm. Sci.</i> 4:49-59, Elsevier Science B.V. (1996) | |
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| Y0 | HB | HE, K., <i>et al.</i> , "Inactivation of Cytochrome P450 3A4 by Bergamottin, a Component of Grapefruit Juice," <i>Chem. Res. Toxicol.</i> 11:252-259, American Chemical Society (1998) | | |
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| | | | | Art Unit | 1626 |
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| YD | HL | LEFEBVRE, I., <i>et al.</i> , "Mononucleoside Phosphotriester Derivatives with S-Acyl-2-thioethyl Bioreversible Phosphate-Protecting Groups: Intracellular Delivery of 3'-Azido-2',3'-dideoxythymidine 5'-Monophosphate," <i>J. Med. Chem.</i> 38:3941-3950, American Chemical Society (1995) | |
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| | | | | First Named Inventor | Serge Boyer |
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| | | | | Examiner Name | Solola, Taofiq A. |
| Sheet | 7 | of | 10 | Attorney Docket Number | 2358.0180002/RWE/AES |

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| Yo | HV | MEYER, R., <i>et al.</i> , "2'-O-Acyl-6-thioinosine Cyclic 3',5'-Phosphates as Prodrugs of Thioinosinic Acid," <i>J. Med. Chem.</i> 22:811-815, American Chemical Society (1979) | | | |
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| YD | IF | OGG, M., <i>et al.</i> , "A reporter gene assay to assess the molecular mechanisms of xenobiotic-dependent induction of the human CYP3A4 gene <i>in vitro</i> ," <i>Xenobiotica</i> 29:269-279, Taylor & Francis Ltd. (1999) | | |
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| | | | | Art Unit | 1626 |
| | | | | Examiner Name | Solola, Taofiq A. |
| Sheet | 9 | of | 10 | Attorney Docket Number | 2358.0180002/RWE/AES |

| NON PATENT LITERATURE DOCUMENTS | | | |
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| Examiner Initials* | Cite No. ¹ | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume number, publisher, city and/or country where published | T ² |
| YD | IP | SHAW, J.-P. and Cundy, K.C., "Biological Screens of PMEA Prodrugs," <i>Pharm. Res.</i> 10:S-294, Kluwer Academic Publishers B.V., Abstract No. PDD 7480 (1993) | |
| | IQ | SHIH, Y.-E., et al., "Preparation and Structures of 2-Dimethylamino-4-phenyl-1,3,2-dioxaphosphorinane-2-oxides," <i>Bull. Inst. Chem., Academia Sinica</i> 41:9-16, Academia Sinica, Nankang, Taipei, Taiwan (1994) | |
| | IR | STARRETT, Jr., J.E., et al., "Synthesis, Oral Bioavailability Determination, and <i>in Vitro</i> Evaluation of Prodrugs of the Antiviral Agent 9-[2-(Phosphonomethoxy)ethyl]adenine (PMEA)," <i>J. Med. Chem.</i> 37:1857-1864, American Chemical Society (1994) | |
| | IS | THOMSON, W., et al., "Synthesis, Bioactivation and Anti-HIV Activity of the Bis(4-acyloxybenzyl) and Mono(4-acyloxybenzyl) Esters of the 5'-monophosphate of AZT," <i>J. Chem. Soc. Perk. Trans.</i> 1,1239-1245, Royal Society of Chemistry (1993) | |
| | IT | VALENTINE, Jr., D., "Preparation of the Enantiomers of Compounds Containing Chiral Phosphorus Centers," <i>Asymmetric Synthesis</i> 4:263-312, Academic Press, Inc. (1984) | |
| | IU | VENOOK, A., "Treatment of Hepatocellular Carcinoma: Too Many Options?," <i>J. Clin. Oncol.</i> 12:1323-1334, American Society of Clinical Oncology (1994) | |
| | IV | VO-QUANG, Y., et al., "(1-Amino-2-propenyl)phosphonic Acid, an Inhibitor of Alanine Racemase and D-Alanine:D-Alanine Ligase," <i>J. Med. Chem.</i> 29:579-581, American Chemical Society (1986) | |
| | IW | WAGNER, A., et al., "Direct Conversion of Tetrahydropyranylated Alcohols to the Corresponding Bromides," <i>Tetrahedron Lett.</i> 30:557-558, Pergamon Press plc (1989) | |
| | IX | WALLACE, E.M., et al., "Design and Synthesis of Potent, Selective Inhibitors of Endothelin-Converting Enzyme," <i>J. Med. Chem.</i> 41:1513-1523, American Chemical Society (1998) | |
| | IY | WALSH, E., et al., "Phenoxyethylphosphonic Acids and Phosphonic Acid Ion-exchange Resins," <i>Phenoxyethylphosphonic Acid Ion-Exchange Resins</i> 78:4455-4458, American Chemical Society (1956) | |

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| Examiner Signature | T. A. Solola | Date Considered | 3-2-06 |
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| | | | | Application Number | 10/698,928 |
| | | | | Filing Date | October 31, 2003 |
| | | | | First Named Inventor | Serge Boyer |
| | | | | Art Unit | 1626 |
| | | | | Examiner Name | Solola, Taofiq A. |
| | | | | Attorney Docket Number | 2358.0180002/RWE/AES |
| Sheet | 10 | of | 10 | | |
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| Examiner Initials* | Cite No. ¹ | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume issue number(s), publisher, city and/or country where published | | | |
| YD | IZ | WATKINS, P., "Noninvasive tests of CYP3A enzymes," <i>Pharmacogenetics</i> 4:171-184, Lippincott Williams & Wilkins (1994) | | | |
| | JA | WEBER, G.F. and Waxman, D.J., "Activation of the Anti-cancer Drug Ifosfamide by Rat Liver Microsomal P450 Enzymes," <i>Biochem. Pharm.</i> 45:1685-1694, Pergamon Press Ltd. (1993) | | | |
| | JB | WEIBEL, M., <i>et al.</i> , "Potentiating Effect of {2-[2-[(2-Amino-1,6-Dihydro-6-Oxo-9H-Purin-9-yl)Methyl]-Phenyl] Ethenyl}-Phosphonic Acid (MDL 74,428), A Potent Inhibitor of Purine Nucleoside Phosphorylase, on the Antiretroviral Activities of 2',3'-Dideoxyinosine Combined to Ribavirin in Mice," <i>Biochem. Pharmacol.</i> 48:245-252, Elsevier Science Ltd. (1994) | | | |
| | JC | WILEMAN, T., <i>et al.</i> , "Receptor-mediated endocytosis," <i>Biochem. J.</i> 232:1-14, Portland Press (1985) | | | |
| | JD | YU, L. J., <i>et al.</i> , "In vivo Modulation of Alternative Pathways of P-450-Catalyzed Cyclophosphamide Metabolism: Impact on Pharmacokinetics and Antitumor Activity," <i>J. Pharmacol. Exp. Ther.</i> 288:928-937, The American Society for Pharmacology and Experimental Therapeutics (1999) | | | |
| | JE | ZON, G., "Cyclophosphamide Analogues" in <i>Progress in Medicinal Chemistry</i> , Ellis, G.P., <i>et al.</i> , eds., Elsevier Biomedical Press, Chapter 4, pp. 205-246 (1982) | | | |
| | JF | ZON, G., <i>et al.</i> , "NMR Spectroscopic Studies of Intermediary Metabolites of Cyclophosphamide. A Comprehensive Kinetic Analysis of the Interconversion of <i>cis</i> - and <i>trans</i> -4-Hydroxycyclophosphamide with Aldophosphamide and the Concomitant Partitioning of Aldophosphamide between Irreversible Fragmentation and Reversible Conjugation Pathways," <i>J. Med. Chem.</i> 27:466-485, American Chemical Society (1984) | | | |
| | JG | International Search Report for related International Application No. PCT/US03/34690, European Patent Office, Netherlands, mailed April 26, 2004 | | | |
| | JH | Copy of Office Action for co-pending United States Application No. 10/698,924, Reddy, K.R., <i>et al.</i> , filed October 31, 2003, mailed June 22, 2005 | | | |
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